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Is Halogen Bonding the Basis for Iodothyronine Deiodinase Activity?

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Density functional theory studies of S···X and Se···X (X = Br, I) halogen-bonding interactions are used to interpret the selection of selenium and iodine for thyroid hormone signaling. A new mechanism for dehalogenation in terms of halogen bonding is proposed. The activation barriers for deiodination of an aromatic iodide by MeSeH and MeSH (17.6 and 19.8 kcal/mol) are consistent with the relative rates of deiodination by iodothyronine deiodinase and its cysteine mutant.

Intermolecular halogen-bonding (XB) interactions[1−4] are of growing importance to crystal engineering[2] and rational drug design[3] based on molecular recognition between biomolecules.[4] The ability of halogens and other electron-rich centers to act as Lewis acidic acceptors is attributed to a positive region found in the electrostatic potentials of CH_3X on the surface of the halogen coaxial with the C−X bond (σ hole).[5] The Pharmacore-based design of mimetics of the iodine-containing thyroid hormones[6] has taken advantage of XB-based recognition in receptors and transport proteins (for example, an I···O interaction in transthyretin).[7] Bromine analogues have been designed to target these interactions as potential treatments for hyperthyroidism[8] and amyloidogenesis.[9] Antithyroid drugs and other Lewis bases have also been shown to form strong XB interactions with I_2.[10] However, it is not clear whether XB plays a role in the activity of the iodothyronine deiodinase (ID) family of selenoenzymes (Scheme 1), which mediate activation of the thyroid hormones [e.g., thyroxine (3,5,3′,5′-tetraiodothyronine, T4 in Scheme 1a)] through the cleavage of C−I bonds.[11] Despite the biological significance of this process, the description of the molecular mechanism for ID is limited to the overall ping-pong kinetics.[11] Complicating elucidation of the reaction mechanism is the difficulty in isolating these membrane proteins. Adaptation into a critical biochemical pathway of not one, but two, trace elements that form a direct bond is an additional question of interest to bioinorganic chemistry. In this Communication, we report density functional theory (DFT) calculations that may link the concept of XB to the activity of the ID enzymes and the selection of selenium and iodine for this critical biological process.

Short S···I and Se···I XB interactions (1.0 Å smaller than the sum of the van der Waals radii) were observed in crystal structures of mutants of the T4 lysozyme with halogenated benzenes (Scheme 1b).[12] The geometries of complexes of Me_2Y (Y = S, Se) with iodides PhI and C_6F_5I based upon these structures have been optimized as the initial conceptual models for ID at the DFT(B3PW91)/BSI level using the *PQS* software package.[13] Interatomic S···I and Se···I distances (Table 1) for the perfluorinated iodobenzene complexes were consistent with the interactions with (seleno)methionine [(Se)Met] in the cavity of the T4 lysozyme mutants (3.0 Å).[12] The formation of these complexes is energetically favorable by −1.3 to −5.0 kcal/mol (ΔE + ZPE), in agreement with previous studies of other XB pairs.[14] The electron-withdrawing fluoro groups enhance XB such that ΔE + ZPE is greater than that of complexes with PhI and a truncated model of thyroxine [1,4-dihydroxo-2,6-diiodobenzene (**1**); Scheme 1c]. Each of these small models maintains the near 180° Y−C−X angle generally observed for XB interactions and indicative of donation from the S/Se p-like lone pair to the σ hole of the halide. Models using MeSeH to represent the selenocysteine (SeCys) residue in the active site of ID produce weaker complexes with **1** (Table 1) because of the lower nucleophilicity of the monomethylated selenium center. Deprotonation of the selenol strengthens the complex

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Scheme 1. (a) Mechanism for ID-1-Mediated Deiodination of Thyroxine, (b) Space-Filling Model of the Interaction of C_6F_5I with SeMet in the T4 Lysozyme Mutant,[12] and (c) Truncated Model for Thyroxine

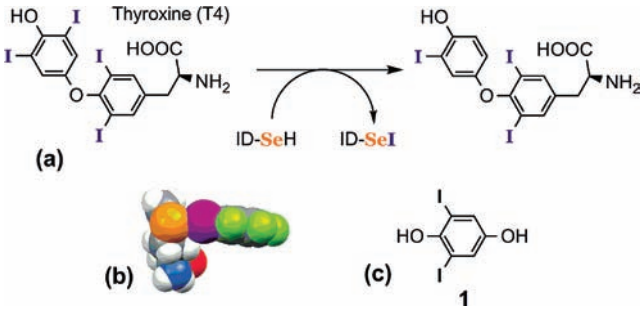

Table 1. Optimized Geometries [DFT(B3PW91)/BSI], Energies of Complex Formation (ΔE + ZPE), and NBO Donor−acceptor Energies ($\Delta E_{D\rightarrow A}$) for Model Complexes

complex	d(Y···X), Å	d(C−X), Å	ΔE + ZPE, kcal/mol	$\Delta E_{D\rightarrow A}$, kcal/mol
$Me_2S\cdot C_6F_5I$	3.246	2.112	−4.1	10.9
$Me_2Se\cdot C_6F_5I$	3.271	2.125	−5.0	14.7
$Me_2S\cdot C_6H_5I$	3.515	2.115	−1.3	5.2
$Me_2Se\cdot C_6H_5I$	3.542	2.120	−1.7	7.3
$Me_2S\cdot$ **1**	3.434	2.123	−1.6	6.6
$Me_2Se\cdot$ **1**	3.462	2.129	−2.7	9.0
MeSeH·**1**	3.571	2.122	−1.8	6.5
$[MeSe]^-\cdot$ **1**	2.947	2.283	−28.4	39.3
$Me_2S\cdot C_6H_5Br$	3.563	1.916	−0.3	2.8
$Me_2Se\cdot C_6H_5Br$	3.634	1.918	−0.5	3.4

(ΔE + ZPE = −28.4 kcal/mol) and shortens the Se···I interaction (2.947 Å).

XB generally has the net effect of lengthening or activating the R−X bond,[15] although exceptions have been noted.[16] The XB donor−acceptor (DA) interaction of a Lewis base with the R−X bond may be described using resonance structures analogous to a hypervalent three-center four-electron bond (eq 1) as discussed previously for Se···N,O interactions.[17] A stronger Lewis base increases the contribution of the right-hand structure to the resonance hybrid and weakens the R−X bond. Within molecular orbital (MO) theory, the XB DA interaction results from mixing of the lone-pair orbital fragment of the Lewis base with the σ^* R−X bond of the acceptor. XB is strengthened when the donor and acceptor orbital fragments are similar in energy, by either destabilizing the lone pair (stronger Lewis base) or incorporating a heavier halogen (weaker R−X bond). For complexes of the thyroxine model **1** with Me_2Y and MeSeH, the C−I bond distance increases by 0.01−0.02 Å, consistent with the weak DA interaction. The strongly nucleophilic $[MeSe]^-$ donor strongly activates the C−I bond (+0.14 Å). In all of these results, the less-nucleophilic sulfur compounds form weaker complexes and are less effective in activating the C−I bond, hence the incorporation of selenium into the ID enzymes.

$$B:X-R \leftrightarrow B-X^+R^- \quad (1)$$

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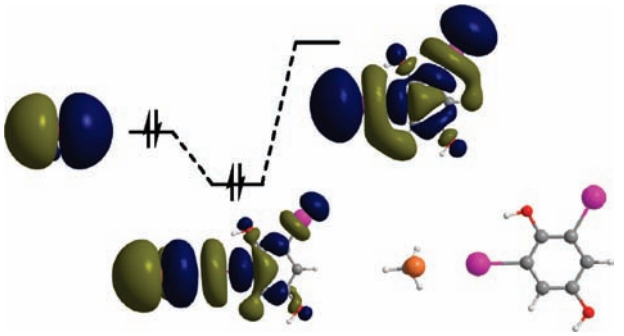

Figure 1. MO diagram for the XB DA interaction in $[MeSe]^-\cdot$ **1**.

The strengths of the XB interactions for the ID models in Table 1 were analyzed using natural bond orbital (NBO) theory,[18] which estimates the energy of the DA interaction ($\Delta E_{D\rightarrow A}$) through localization of the MOs. Complexes with Me_2Y and MeSeH as donors are generally weak ($\Delta E_{D\rightarrow A}$ = 5−15 kcal/mol), with the highest values for the perfluorinated iodobenzenes where the electron-withdrawing groups decrease the energy of the C−I σ^* MO. Deprotonation of MeSeH increases the energy of the p-type lone-pair donor MO for a strong interaction with the C−I σ^* MO of **1** ($\Delta E_{D\rightarrow A}$ = 39.3 kcal/mol). The Se−I bonding MO of $[MeSe]^-\cdot$ **1** and its parent fragment MOs are shown in Figure 1. Consistent with the DA bonding models, the magnitude of $\Delta E_{D\rightarrow A}$ correlates with activation of the C−I bond.

Extension of the NBO analysis may shed light on the selection of iodine over more common halogens for thyroid function. The geometries and interaction energies were determined for complexes of Me_2Y with PhBr. (No bound complex could be found for PhCl.) As in the T4 lysozyme study, the interatomic Y···Br distances are longer than those of iodine and the DA interactions are weaker (Table 1). These results are consistent with the higher-energy antibonding MOs of the stronger C−Cl and C−Br bonds [for CH_3X, ε_{CX^*} = 0.0064 au (Cl), −0.0177 au (Br), and −0.0402 au (I)]. In addition, the DFT reaction energies for dehalogenation of PhX by MeYH are lower for the sulfur and bromine versus selenium and iodine for an overall trend in ΔE + ZPE for the formation of chalcogenyl halides (RYH + PhX → RYX + PhH) of S−Br < S−I < Se−Br < Se−I (0.2, −4.2, −8.6, and −12.0 kcal/mol, respectively). Thus, whereas most arguments for the selection of iodine in thyroid hormones are centered around its large spherical shape,[11] these results suggest that iodine's propensity for XB and the energetic favorability of reductive deiodination, especially by selenium, relative to more abundant halogens are underlying factors in its selection for thyroid function.

The prevalence of XB in thyroid hormone transport and recognition pathways suggests a role for these interactions in the mechanism of ID. Although weak XB interactions (typically O···I) are present in thyroid transport proteins, ID employs a highly nucleophilic selenium. Given the XB interactions between the selenium compounds and the aryl iodides in Table 1, we propose the mechanism in Figure 2a which incorporates the DA model of XB into C-I activation by ID. The substrate binds to the ID active site and forms a weak XB interation with the selenol SeCys. Deprotonation of the selenol by an active site base strengthens the Se···I interaction

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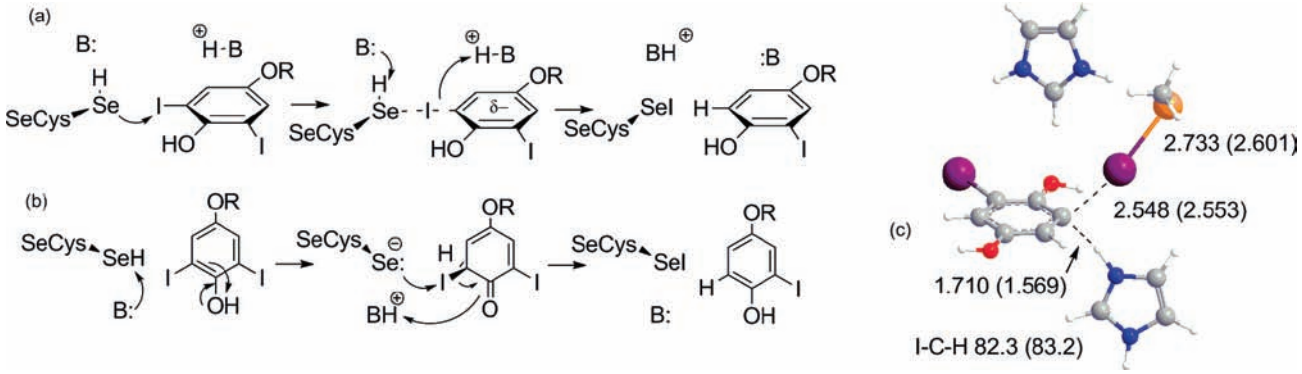

Figure 2. Mechanisms for deiodination by ID: (a) XB-based; (b) tautomer-based; (c) DFT(B3PW1)/BSII transition state for XB-based deiodination (B = Im) of **1** by $[MeSe]^-$ ($[MeS]^-$).

halogen-bonded intermediate and activates the C−I bond. A proton donor stabilizes the accumulation of negative charge on the ring to increase the admixture of the right-hand resonance structure in eq 1 and cleave the C−I bond.

This XB-based mechanism stands in contrast with previous dehalogenation mechanisms, which activate the C−I bond through tautomerization to the keto form of the phenol (Figure 2b).[19] Geometry optimization of this keto intermediate does indeed show activation of the C−I bond (+0.15 Å), but disruption of aromaticity destabilizes the tautomer by ∼15 kcal/mol. Further, certain ID enzymes and simple selenium and tellurium reagents deiodinate the inner ring of thyroid hormones[11] and iodinated methoxybenzoates,[19] respectively, for which a tautomer cannot be drawn. The means by which the protein forces the tautomerization is also unclear.

The XB-based mechanism in Figure 2a was modeled by adding two imidazole (Im) groups to the $[MeSeH]\cdot$**1** complex: one to act as the active site base and stabilize the selenolate anion formed upon deprotonation and a second, protonated, to serve as the proton donor. Im groups are used as the model proton donor/acceptors because their basic forms are neutral and their potential for hydrogen bonding is limited. These groups are not analogues of critical His residues found in the protein.[20] In the DFT(B3PW91)/BSII-optimized structure of this model, hydrogen bonding between Im and MeSeH strengthens the Se···I interaction relative to $[MeSe]\cdot$**1** [d(Se···I) = 3.249 Å; d(C−I) = 2.153 Å]. Deprotonation of this reactant complex is uphill by 9.6 kcal/mol with an XB interaction similar to $[MeSe]^-\cdot$**1** [d(Se···I) = 3.026 Å; d(C−I)=2.285 Å]. From this intermediate, the transition state was determined by following the C−I bond-breaking coordinate. The fully optimized structure occurs 17.6 kcal/mol ($\Delta G^{\ddagger}$) above the reactant complex when the C−I bond has increased by 0.31 Å and the Se−I distance has decreased to 2.733 Å (Figure 2c). The iodine distorts out of the plane of the ring as the proton is transferred to the carbon, but there is no distortion in the ring to indicate a loss of aromaticity. In contrast, replacement of selenium with sulfur has a higher $\Delta G^{\ddagger}$ (19.8 kcal/mol), roughly consistent with the 100-fold reduction in ID activity for Cys mutants.[11] The sulfur transition state occurs later along the reaction coordinate [d(C−I) = 2.553 Å; d(C−H) = 1.569 Å] as a result of the weaker S···I interaction in the reactant complex [d(S···I) = 3.215 Å; d(C−I) = 2.138 Å].

In summary, analysis of XB in a series of complexes suggests that the occurrence of selenium and iodine in the thyroid results from a synergistic effect of the nucleophilicity of selenium and the relative weakness of the C−I bond. The DA model of XB provides a mechanism for deiodination by ID enzymes and potentially for nucleophilic reductive dehalogenation in general. Extension of the XB concept to the reactivity of ID should provide new avenues for the design of antithyroid agents.

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Supporting Information Available: Theoretical methods and Cartesian coordinates of the complexes in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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